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INFLUENCE OF THE DRUGS USED IN THERAPY ON THE ACTION OF THE CURARIFORM SUBSTANCES

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In surgical practice, the increasingly frequent use of old and new substances for therapeutic action of the most diverse kinds has created innumerable problems, one of the most important of which is certainly the influence of drugs on the action of the myorelaxing substances.

In fact, the curariform effect of normal doses of pachycurares and leptocurares can be modified considerably by the simultaneous administration of any therapeutic substance which, as a side effect, has the capacity to interfere with transmission of a nerve stimulus.

The anesthetist may not ignore the serious harm deriving from such possible associations of drugs.

Much experimental and clinical work in the medical literature calls attention to the capacity of some drugs to interfere with the effects of the curariforms.

Indeed, there are a great many descriptions of muscular paralyses occurring during and after operations, deriving from the therapeutic use of such substances, such as antibiotics, vitamins, anticholinesterases, antimitotics, and local anesthetics.

It is important for the anesthetist to be familiar with these pharmacological actions because many surgical patients receive generous doses of such drugs before, during, and after the operation.

Moreover, knowledge of these facts can prevent or resolve those syndromes in which the simultaneous administration of substances with a neuromuscular effect and of myorelaxant substances have caused respiratory paralyses of long duration through overdose or synergy.

The principal mechanisms through which a substance can develop a pharmacological action at the level of the neuromuscular junction are essentially three: alteration of the sensitivity of the motorial plate, alteration of the liberation or metabolism of acetylcholine, alteration of the metabolism and of the elimination of curariform substances.

Very often, the neuromuscular impulse inhibition mechanism involves two or more actions together.

Antibiotics

Several antibiotics (streptomycin, dihydrostreptomycin, neomycin, viomycin, paromomycin, polymyxin, colistin, kanamycin) impede

neuromuscular transmission through a curariform effect (Brazil, Corrado, Adamson, Marshall, Kownacki).

As regards penicillin G and tetracyclin, it has been established (Timmerman, Long, Pittinger) that they have no curariform effects, but other authors (Baisset, Lareng, Puig) have demonstrated experimentally that these substances too potentiate d-tubocurarine.

Although the neuromuscular action of the antibiotics (Lullmann, Renter) amounts only to 1/200-1/2,000 of the action of d-tubocurarine, in therapy this quantitative difference is partly cancelled out by the high doses of antibiotics administered.

Many cases have been described in which intraperitoneal or intrapleural administration of neomycin or steptomycin was responsible for postoperative apnea (Pridgen, Engel, Denson, Pittinger, Doremus).

Sometimes the quantity of antibiotics administered exceeded the maximum safe dose, but in other cases a relatively small dose markedly potentiated the action of curarine.

Numerous experimental data confirm the curarizing property of antibiotics and the potentiation of the actions of myorelaxants. The neuromuscular block caused by streptomycin and neomycin appears to be of a competitive type: in fact, it is potentiated by the competitive curares and by ether and is neutralized by neostigmine (Pittinger, Long, Miller).

The curarization of tetracyclin presents competitive-block characteristics but also depolarizing-block characteristics. Kanamycin and polymyxin B are depolarizers inasmuch as the anticholinesterases potentiate the neuromuscular block induced by them.

The antagonism found experimentally between the anticholinesterases and paralysis developed through the use of antibiotics has not always been appreciated in the clinic (Kownacki, Bush, Bodley, Meirsman-Roobroeck).

Fortunately, muscular paralysis developed through the use of antibiotics is spontaneously reversible with time.

The use of those antibiotics (penicillin, chloramphenicol, erythromycin, oleandomycin, ristocetin) which have appeared to lack curariform action is advisable.

Thiamine

The neuromuscular-block action of thiamine has been ascertained by a great deal of experimental work carried out on various animal species (Cheymol, Bourillet, Levassort, Kerp, Di Palma, Gjone, Minelli, Ngai, Ginsburg, Katz).

The derivatives of thiamine (cocarboxylase, acetylthiamine, thiamine disulfide, thiamine dithiopropyl, oxythiamine, pyrithiamine) also present, albeit with some differences, substantiall, the same properties. Thiamine (which in physiological doses is indispensable

for nerve impulses) and its derivatives, in large doses, inhibit neuromuscular transmission in animals and man.

The curarization of thiamine is of brief duration (10-20 minutes), is spontaneously reversible, and is proportional to the dose used.

The neuromuscular block which occurs seems to be of the competitive type (although differing in certain respects) and is neutralized by neostigmine.

In man, thiamine in large doses (40-80 mg/kg intravenously) has its own curariform action, while in smaller doses it considerably potentiates muscular paralysis developed by myorelaxants (De Castro, Mundeleer).

Pantothenic Acid

As is known, pantothenic acid plays a part in the constitution of coenzyme A and forms part of the acetylation enzyme which produces acetylocholine.

In man, pantothenic acid has shown distinct anticuraric properties: injected intravenously in doses of 1,000-1,500 mg, it is an effective antidote to the competitive curares (Galeotto, Rizzi, Weber).

The antagonism is manifested 4-6 minutes after administration.

Pituitrin

It has been pointed out that prolonged infusion of pituitrin alters sensitivity of the motorial plate in relation with the depolarizing myorelaxants, so that neuromuscular blocks of long duration can be produced, recovery from which can be achieved by means of neostigmine (Hodges, Bennet, Tunstall, Shanks).

These observations have not been confirmed. Nevertheless, it can be held that the altered sensitivity of the motorial plate is consequent upon an overdose of depolarizing myorelaxant, which in these cases should be used with caution.

Ganglioplegics

These drugs compete with acetylcholine at the level of the cholinergic receptors of the neuromuscular junction.

Hexamethonium -- Pentamethonium and hexamethonium in large doses cause a neuromuscular block of competitive type, neutralized by the anticholinesterases.

Therefore, they potentiate d-tubocurarine (Deacok, Davies) and are antagonistic to the depolarizing agents.

Arfonad -- This drug produces a weak neuromuscular block of competitive type and potentiates the competitive myorelaxants.

In addition, since arfonad is probably destroyed by the cholinesterases (Tewfich), it may be a cause (Pearcy, Wittenstein) of a

potentiation of succinylcholine; therefore it is advisable not to use the two substances simultaneously.

Mecamylamine -- Mecamylamine in itself has a weak curariform action (Stone, Torchiana, Navarro) and considerably potentiates (by raising the threshold of excitability of the motorial plate or by inhibiting synthesis of acetylcholine) the effects of d-tubocurarine (Payne).

When mecamylamine is administrated before depolarizing myorelaxants, it results in a neuromuscular block with nondepolarizing characteristics and is neutralized by neostigmine (Bennet, Tyler, Zaimis).

Bretylium salts -- This substance too potentiates the neuromuscular-block action of d-tubocurarine (Dixit, Gulati, Gokhale).

Quinine and Quinidine

Quinine exercises a double action on the striated muscle: a direct action on the fibrocellular tissue and a curariform type of action on neuromuscular transmission.

In a different manner from curare, quinine acts directly on the muscular fibrocellular tissue, depressing its contractibility or lengthening its refractory phase.

In a manner analogous to curare, quinine reduces the excitability of the motorial plate and reduces or nullifies the muscular response to acetylcholine. Schmidt, Vick, and Sadove have observed that quinidine administered after d-tubocurarine greatly potentiates its effect: they describe the case of a patient who underwent surgery for a hiatus hernia and who had received 7 mg of d-tubocurarine.

At the conclusions of the operation, the rise of an atrial fibrillation called for the administration of 200 mg of quinidine: within 15 minutes, the symptoms of curarization reappeared, going as far as respiratory paralysis, which was maintained for nearly 3 hours.

The significance and clinical importance of this observation are obvious if one thinks of the frequent use of quinidine to correct cardiac arrhythmia arising during or after general anesthesia.

Experimental research carried out on the rabbit has demonstrated a synergism of action between quinidine and curare: after curarization (achieved through the use of either competitive or depolarizing myorelaxants), administration of quinidine makes muscular relaxation reappear, with respiratory paralysis in a different degree.

When quinidine is introduced before myorelaxants, the response to them is not altered either quantitatively or qualitatively.

Anticholinesterases

As is known, these drugs inhibit the cholinesterases intended for destruction of acetylcholine: their principal pharmacological effect will be brought about by an accumulation of acetylcholine.

The compounds commonly used in therapy (neostigmine, tensilon) also possess their own motorial-plate depolarizing action (Wescoe, Riker).

Organophosphoric esters -- The chemical family of the anti-cholinesterasic compounds also includes the organophosphoric esters, compounds which are not used in therapy but are capable, because of their multiple uses in everyday life, of producing serious poisoning (Fischetti).

These compounds, initially developed as wartime weapons, have found practical application as insecticides because of the outstanding results obtained.

The organophosphoric esters, which include the orthodithiophosphates (Malathion), the aminofluorophosphates, the pyrophosphates (TEPP [tetraethylpyrophosphate], DFP (di-isopropylfluoro-phosphate) and others, all potent insecticides, possess as their principal pharmacological action the capacity to inhibit the enzymatic system of the cholinesterases.

The neuromuscular apparatus will experience the "nicotinic" actions of these substances by reacting to the accumulation

of acetylcholine at the level of the motorial plate first of all with a stimulus to contraction, and then with loss of the capacity to contract, going as far as paralysis. On the subject of human therapy, for removal of the effects attributable to the nicotinic action of the organophosphoric esters, myorelaxants have also been made use of in order to achieve control of the motor manifestations.

The use of d-tubocurarine (competitive curare) has been proposed for neutralizing neuromuscular depolarization effects. However, the use of myorelaxants may not be entirely without disadvantages in view of a possible summation of effects obtainable through the use of a depolarizing agent and a competitive agent.

Leroy and Colle describe a case of apnea lasting 4 hours, consequent upon the use of 50 mg of succinylcholine in a patient with a presumed subacute intoxication by E 605.

Tetrahydroaminoacridine (THA) -- THA is a potent anticholinesterase: it is used in cases of intractable pain together with morphine in order to avoid respiratory depression.

The anticholinesterasic effect of THA has also been used to prolong the action of succinylcholine and to neutralize d-tubocurarine, so long as a complete antagonist of the competitive myorelaxants has not been revealed (Benveniste, Dyberg).

Dimethylurethymine (AB-132) -- Wang and Ross have described two cases of prolonged apnea consequent upon the use of succinylcholine in patients subjected to anticancer therapy with antimitotics. In one patient, who died the following day, the administration of 80 mg of succinylcholine caused an apnea of 7 hours. Another patient had an apnea of 1 hour, fortunately terminated, after the introduction of 20 mg of succinylcholine.

The respiratory insufficiency is connected with inhibition of the cholinesterases caused by an antimitotic (AB-132) administered to patients as a preoperative treatment.

Successive experiments made it clear that repeated treatment with this substance (0.5 g per diem) reduces the level of the cholinesterases to less than 20% of their normal value.

The activity of a true cholinesterase returns to normal after 30-40 days from cessation of therapy with AB-132.

Therefore, this drug is a powerful inhibitor of the cholinesterases, similar to di-isopropyl-pyrophosphate, in that the inhibition of the cholinesterases is irreversible and of long duration.

Procaine

Procaine possesses a distinct curariform effect (Niljestrand, Magnus, Fulton, Harvey).

Procaine and other local anesthetics inhibit the liberation of acetylcholine at the level of the motorial plate (Harvey), therefore potentiating the action of the competitive curares.

However, the action of procaine at the level of the neuromuscular junction is complex: being destroyed by plasmatic cholinesterase if used after the depolarizing curares, it can prolong their effect, while there is antagonism if the procaine is administered first (Ellis, Wnuck, De Beer, Foldes).

As regards d-tubocurarine, procaine always potentiates its effect.

Magnesium

The principal effect of magnesium ions is to decrease the quantity of acetylcholine liberated at the passage of the nervous impulse. They also decrease the motorial plate's sensitivity to acetylcholine and the direct excitability of the muscular fiber.

The magnesium ions potentiate the action of the competitive curares, which in turn potentiate the action of magnesium (Del Castillo, Engbaek).

Calcium ions neutralize the neuromuscular block produced by magnesium.

Barbiturates

The barbiturates influence neuromuscular transmission (Gross, Cullen), probably through a central effect and through an action on the muscle, and potentiate the competitive curares.

It seems that the barbiturates neutralize the anticuraric effect of neostigmine (Sirnes).

It is well to keep these data in mind when the patient has received large doses of barbiturate.

Conclusions

This brief review, even though incomplete, has brought out the fact that many drugs have curariform effects as a collateral action, or can profoundly modify the organism's response to the curares.

Therefore, the anesthetist should have sound pharmacological knowledge and should keep up to date on the pharmacology of the new compounds.

When a patient is to be subjected to anesthesia with use of myorelaxants, an accurate evaluation of the preoperative therapeutic measures taken should always be carried out.

Knowledge of these data will be valuable for the purpose of preventing or resolving the so-called prolonged curarizations which are resistant to the anticholinesterases.

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